show changes made." For the convenience of the Examiner, the claims that will be pending upon entry of the instant Amendment are attached hereto as Appendix B.

Claim Rejections

Rejection of Claims 1-4 and 10-14 Under 35 U.S.C. § 102

The Examiner has rejected claims 1-4 and 10-14 under 35 U.S.C. § 102(a) as being anticipated by Takada *et al.* The Examiner has also rejected claims 1-2, 4, 6, 10-11, 13, 14, and 17 under 35 U.S.C. § 102(b) as being anticipated by Yee *et al.*

Applicants respectfully traverse the foregoing rejections. However, in the interest of expediting prosecution, and in no way conceding to the validity of the rejections, claims 1 and 10 have been amended rendering the foregoing rejections moot. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejections.

Rejection of Claims Under 35 U.S.C. § 102 (e)

Rejection of Claims 1-3, 5, 8, and 10-14 Under 35 U.S.C. § 102 (e)

The Examiner rejected claims 1-3, 5, 8, and 10-14 under 35 U.S.C. § 102 (e) as being anticipated by Schreier *et al.*

Applicants respectfully traverse the foregoing rejection. Applicants submit that the rejection no longer applies to claims 1-3, 5, 8, and 10-14 as amended herein. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 1-2, 4-8, 10-11, 13-15, and 20 Under 35 U.S.C. § 102(e)

The Examiner has rejected claims 1-2, 4-8, 10-11, 13-15, and 20 under 35 U.S.C. § 102(e) as being anticipated by Kraus *et al.*

Applicants respectfully traverse the foregoing rejection. Applicants submit that the rejection no longer applies to claims 1-2, 4-8, 10-11, 13-15, and 20 as amended herein. In particular, because the Kraus *et al.* patent does not teach the use of an Ebola transmembrane form of viral glycoprotein or derivative thereof, Applicants respectfully

submit that the Kraus *et al.* patent does not anticipate the claimed invention. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 1-2, 4, 10-11, 13-17, and 20 Under 35 U.S.C. § 102(e)

The Examiner has rejected claims 1-2, 4, 10-11, 13-17, and 20 under 35 U.S.C. §102(e) as being anticipated by Cohen-Haguenauer *et al.*

Applicants respectfully traverse the foregoing rejection. Applicants submit that the rejection no longer applies to claims 1-2, 4, 10-11, 13-17, and 20 as amended herein. In particular, because the Cohen-Haguenauer *et al.* patent does not teach the use of an Ebola transmembrane form of viral glycoprotein or derivative thereof, Applicants respectfully submit that the Cohen-Haguenauer *et al.* patent does not anticipate the claimed invention. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 1-2, 4-5, 8, 10-11, 13-16, and 18 Under 35 U.S.C. § 102(e)

The Examiner has rejected claims 1-2, 4-5, 8, 10-11, 13-16, and 18 under 35 U.S.C. § 102(e) as being anticipated by Bodner *et al.*

Applicants respectfully traverse the foregoing rejection. Applicants submit that the rejection no longer applies to claims 1-2, 4-5, 8, 10-11, 13-16, and 18 as amended herein. In particular, because the Bodner *et al.* patent does not teach the use of an Ebola transmembrane form of viral glycoprotein or derivative thereof, Applicants respectfully submit that the Bodner *et al.* patent does not anticipate the claimed invention. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 1-2, 4-6, 8, 10-11, 13-15, 19 and 20 Under 35 U.S.C. § 102(e)

The Examiner has rejected claims 1-2, 4-6, 8, 10-11, 13-15, 19 and 20 under 35 U.S.C. § 102(e) as being anticipated by Rooney *et al.*

Applicants respectfully traverse the foregoing rejection. Applicants submit that the rejection no longer applies to claims 1-2, 4-6, 8, 10-11, 13-15, 19 and 20 as amended herein. In particular, because the Rooney *et al.* patent does not teach the use of an Ebola

transmembrane form of viral glycoprotein or derivative thereof, Applicants respectfully submit that the Rooney *et al.* patent does not anticipate the claimed invention. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 1-2, 4-6, 8-11, 13-14, 17 and 20 Under 35 U.S.C. § 102(e)

The Examiner has rejected claims 1-2, 4-6, 8-11, 13-14, 17, and 20 under 35 U.S.C. § 102(e) as being anticipated by Levine *et al.*

Applicants respectfully traverse the foregoing rejection. Applicants submit that the rejection no longer applies to claims 1-2, 4-6, 8-11, 13-14, 17, and 20 as amended herein. In particular, because the Levine *et al.* patent does not teach the use of an Ebola transmembrane form of viral glycoprotein or derivative thereof, Applicants respectfully submit that the Levine *et al.* patent does not anticipate the claimed invention. Therefore, Applicant requests withdrawal of this rejection.

Rejection of Claims 10-20 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 10-20 under 35 U.S.C. § 112, first paragraph as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

The Examiner also cites the *In re Wands* factors to support this rejection.

The Court of Appeals for the Federal Circuit in *In re Wands*, USPQ 2d 1400 (Fed. Cir. 1988) set forth the factors that should be considered when determining whether a disclosure meets the enablement requirement: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims." It is Applicants' position that under these guidelines, the pending claims are fully enabled and satisfy the requirements under 35 U.S.C. §112, first paragraph.

Routine Experimentation and Predictability of the Art

According to the Examiner, the claims are not enabled because of the quantity of experimentation required to perform the claimed methods and the unpredictability of the art. In particular, at page 7 of the Office Action, the Examiner cites references and asserts that:

> [t]he art in the area of gene therapy and immunization using recombinant vectors and constructs is highly unpredictable...The unpredictability in attempting to treat any given disease in humans is augmented by the lack of suitable animal models for most disease conditions in humans and the unpredictability in attempting to reproduce in humans the results obtained in the few animal models that do exist...With regard to recombinant vaccines or immunizing agents targeted to specific cells or tissues, the art is highly unpredictable.

Applicants respectfully traverse the foregoing rejection and respectfully submit that the level of skill in the art in the area of gene therapy and immunization using recombinant vectors and constructs, is quite high, and this technology area is predictable. Applicants submit that the specification discloses ample guidance as to how one of skill in the art would make and use the genetic constructs and methods of the claimed invention. Specifically, Applicants respectfully submit that the instant specification teaches methods for determining, for example, the specificity of Ebola virus glycoproteins (Example 1) and the efficacy of targeting cells with gene transfer vectors (Example 2). Thus, Applicants respectfully submit that while aspects of the field of gene therapy may not be an exact science, the genetic constructs and methods taught by Applicants are sufficiently described to enable an ordinary skilled artisan to make and use the claimed invention using only routine experimentation.

Applicants respectfully further submit that one of skill in the art routinely relies on animal models as a tool for assessing disease conditions in humans. Moreover, a great deal of important work in understanding disease conditions began in animal models and has been successfully applied to humans. One of skill in the art would thus readily appreciate the acceptance of the use of animal models in evaluating and formulating compositions and methods for treating human disease conditions.

Based on the foregoing, Applicants respectfully submit that pending claims fulfill the 35 U.S.C. §112, first paragraph requirements. Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

State of the Art

The Office Action at page 10 indicates that:

> [t]he state of the art with regard to gene therapy and immunization using recombinant genetic constructs-carriers is poorly developed.

Applicants submit that the state of the art with respect to gene therapy and immunization is a growing field which is well-established. The instant specification teaches a genetic construct and methods for using the genetic construct. The Examiner asserts that no successful method of vaccinating humans against any disease using recombinant vectors comprising carriers containing glycoproteins capable of targeting the construct to specific cells had been demonstrated at the time of filing. Applicants respectfully further submit that there is no evidence in the Office Action that would support the conclusion that the specific claimed methods of the present invention would not work as claimed. Applicants respectfully submit that the disclosure of the invention as set forth in the application must be given the presumption of correctness and operativeness by the PTO. *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1967); see also, *In re Bowen*, 492 F.2d 859, 181 U.S.P.Q. 48 (C.C.P.A. 1974). The Office Action however, proffers nothing but conclusory statements to controvert the truth of Applicants' assertion. Thus, it is Applicants' position that the pending claims are fully enabled and satisfy the requirements under 35 U.S.C. §112, first paragraph.

Sufficient Guidance and Direction Have Been Presented and Multiple Working Examples Are Taught By the Present Invention

In assessing the quantity of experimentation necessary and the amount of direction or guidance presented by the instant specification, the Examiner indicates that:

> Applicants present no working examples of the claimed invention...Applicants provide no specific teachings on use of the claimed invention to treat any specific disease or immunize against any given pathogen.

Applicants respectfully submit that the present invention provides more than sufficient guidance and direction as to how to perform the claimed methods. Moreover, Applicants teach multiple working examples which illustrate how the methods of the present invention may be performed. Specifically, Applicants provide genetic constructs and methods for targeting gene transfer vectors to certain cell types by pseudotyping with a transmembrane form of viral glycoprotein (see, page 3, line 4 through page 6, line 24 of the specification). Applicants further disclose suitable formulations for pharmaceutical compositions containing the constructs of the present invention (see, for example, page 6, line 25 through page 7, line 18 of the specification). Applicants submit that the instant application provides multiple working examples with regard to the claimed embodiments. In particular, Applicants describe the production of recombinant retroviruses and provide results relating to the binding of sGP to neutrophils and demonstrate the infection of different cell types by a GP-pseudotyped vector of the present invention (see, for example, Example 1). In addition, Applicants teach methods for determining the efficacy of targeting endothelium with the gene transfer vectors pseudotyped with GP of the present invention (see Example 2). Applicants surprisingly found that in Ebola infection, preferential binding and infection of microvascular endothelial cells may lead ultimately to a loss of capillary integrity that results in the severe hemorrhage observed in the terminal stages of the disease (see Example 1). The differential binding of the two gene products from the same viral structural gene generated by RNA editing suggests that they have evolved functionally to differentially affect immunity and infectivity. Applicants further disclose that the ability to facilitate viral replication and target the virus to endothelial cells by alternative products of the same viral gene represents an efficient genetic mechanism which can account for different pathologic features of this disease, for example, inhibition of sGP binding to neutrophils and GP to endothelium is likely to ameliorate the effects of acute Ebola virus infection (see page 13, lines 5-12 of the specification).

Moreover, Applicants submit that the examiner has the initial burden of establishing a reasonable basis to question the enablement provided for the claimed invention. See *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Furthermore, a requirement for some experimentation does not prevent the satisfaction of the enablement requirement (*Northern Telecom, Inc. v. Datapoint Corp.*, 15 U.S.P.Q.2d1321, 1329 (Fed. Cir. 1990)). As established above, a person of ordinary skill in the art would know how to make and use the claimed invention. Thus, Applicants respectfully request reconsideration and withdrawal of the aforementioned rejection.

Scope of the Invention

The Examiner, at page 4, indicates that "[t]he scope of the invention is broad, reading on gene therapy for any disease and immunization against any pathogen."

Applicants respectfully traverse and submit that one skilled in the art, after reading the specification, could perform the newly claimed methods without undue experimentation and thus the pending claims are fully enabled.

Based on the foregoing, Applicants respectfully submit that pending claims fulfill the 35 U.S.C. §112, first paragraph requirements. Applicants therefore respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims 1-20 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 1-20 under 35 U.S.C. § 112, second paragraph as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." The Office Action further asserts that "[c]laims 1-3 and 10-12 (and dependent claims) are vague in the recitation of the phrase 'viral glycoprotein or derivative thereof' because it is unclear what the term 'derivative thereof' encompasses."

Applicants traverse the foregoing rejection and submit that the pending claims distinctly claim the subject matter which Applicants regard as their invention. The instant specification discloses that "derivatives of the transmembrane glycoprotein which retain the capability of targeting specific cell types, may also be employed, for example, the

transmembrane glycoproteins may be mutated, *e.g.*, toxic regions may be removed to improve producer cell viability (see Figure 10)" (see page 3, lines 28-31 of the specification). Furthermore, the instant specification provides a summary of the characterization of GP and sGP derivatives for their ability to pseudotype to induce cytotoxicity in producer cells, as set forth in Figure 10. Applicants therefore submit that based on the teachings in the specification, one of skill in the art would understand the meaning of the term "derivative thereof." Applicants thus respectfully request that the Examiner withdraw this rejection.

The Examiner is also of the opinion that "[c]laims 1 and 10 are vague in the recitation of the phrase 'gene operatively-linked to a carrier' because it is unclear how the gene is linked to the carrier."

Applicants traverse the foregoing rejection and submit that the meaning of the term "operatively-linked" is clearly taught in the instant specification. Specifically, page 4, lines 3-14 of the specification disclose that:

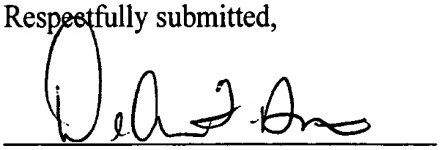
> [t]he term 'operatively-linked' as used herein refers to functional linkage between a nucleic acid expression control sequence (such as a promoter) and a second nucleic acid sequence (*i.e.*, gene), wherein the expression control sequence directs transcription of the nucleic acid corresponding to the second sequence. Expression control sequences are known to those skilled in the art (see, *e.g.*, Goeddel, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA (1990)). 'Associated with' as used herein refers to the transmembrane form of viral glycoprotein being in contact or linkage with the transfer vehicle or carrier in such a way as to direct the transfer vehicle or carrier to certain cell types. The terms 'transfer vehicle' and 'carrier' refer to any type of structure which is capable of delivering the gene of interest to a target cell.

In addition, Applicants teach that "[m]any transfer vehicles or carriers are known in the art. For example, various viruses that are capable of infecting cells can be recombinantly manipulated to carry the gene of interest without affecting their infectivity" (see page 4, lines 14-16 of the specification). In short, Applicants respectfully submit that one of skill in the art after reading the specification, would readily understand how to "operatively-link" the gene of interest with a carrier as claimed by the present invention.

In view of the foregoing, Applicants respectfully submit that the pending claims particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Thus, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

CONCLUSION

Respectfully submitted,



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Dated: February 3, 2003

APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Please cancel claims 2, 3, and 12, without prejudice, and amend claims 1 and 10 as follows:

1. **(Amended)** A genetic construct comprising a gene operatively-linked to a carrier, wherein the carrier is associated with an Ebola [a] transmembrane form of viral glycoprotein or derivative thereof, which is expressed on the surface of the carrier.

10. **(Amended)** A method of targeting a gene to a cell comprising the step of administering to a cell population a genetic construct comprising the gene operatively-linked to a carrier, wherein the carrier is associated with [a] an Ebola transmembrane form of viral glycoprotein or derivatives thereof.

APPENDIX B
PENDING CLAIMS

1. **(Amended)** A genetic construct comprising a gene operatively-linked to a carrier, wherein the carrier is associated with an Ebola transmembrane form of viral glycoprotein or derivative thereof, which is expressed on the surface of the carrier.

4. The genetic construct of Claim 1, wherein the carrier is a viral vector.

5. The genetic construct of Claim 1, wherein the carrier is a non-biologic gene targeting vehicle.

6. The genetic construct of Claim 4, wherein the viral vector is a retroviral vector.

7. The genetic construct of Claim 4, wherein the viral vector is a lentiviral vector.

8. The genetic construct of Claim 5, wherein the non-biologic gene targeting vehicle is a liposome.

9. The genetic construct of Claim 5, wherein the non-biologic gene targeting vehicle is a DNA-protein complex.

10. **(Amended)** A method of targeting a gene to a cell comprising the step of administering to a cell population a genetic construct comprising the gene operatively-linked to a carrier, wherein the carrier is associated with an Ebola transmembrane form of viral glycoprotein or derivatives thereof.

11. The method of Claim 10, wherein the transmembrane form of viral glycoprotein or derivative thereof is expressed on the surface of the carrier.

13. The method of Claim 10, wherein the carrier is a viral vector.

14. The method of Claim 10, wherein the step of administration is *ex vivo*.

15. The method of Claim 10, wherein the step of administration is *in vivo*.

16. The method of Claim 10, wherein the cell is an endothelial cell.

17. The method of Claim 10, wherein the cell is a hepatocyte.

18. The method of Claim 10, wherein the cell is a monocyte.

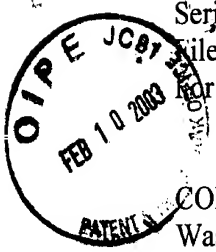
19. The method of Claim 10, wherein the cell is a dendritic cell.

20. The method of Claim 14, further comprising the step of introducing the cell population to a subject.

#1636

In re the application of Gary J. Nabel, *et al.* Case Docket No. UMV-1474US

Serial No. 09/600,766
Filed: July 21, 2000
For: TARGETING GENE TRANSFER VECTORS TO CERTAIN CELL TYPES BY PSEUDOTYPING WITH VIRAL GLYCOPROTEIN



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Sir:

Transmitted herewith for filing in connection with the above-identified application are the following:

☒ Amendment and Response (14 pages including Appendices A and B);
☒ Request for One-Month Extension of Time (1 page, in duplicate);
☒ and return postcard.

The fee has been calculated as shown below:

	(Col. 1)		(Col. 2)	(Col. 3)
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NO. PREVIOUSLY PAID FOR	PRESENT EXTRA
TOTAL	* 17	MINUS	** 20	= 0
INDEP.	* 2	MINUS	*** 3	= 0
☐ FIRST PRESENTATION OF MULTIPLE DEP. CLAIM				

SMALL ENTITY			OTHER THAN A SMALL ENTITY	
RATE	ADDIT. FEE	OR	RATE	ADDIT. FEE
x 9 =	$0.00		x 18 =	$.00
x 42 =	$0.00		x 84 =	$.00
+140 =	$.00		+ 280 =	$.00
TOTAL ADDIT. FEE	$0.00	OR	TOTAL	$0.00

* If the entry in Col 1 is less than the entry in Col. 2, write "0" in Col. 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found from the equivalent box in Col. 1 of a prior amendment or the number of claims originally filed.

☐ A check in the amount of _____ is enclosed for presentation of extra claims.
☐ A check in the amount of _____ is enclosed for .
☒ The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 12-0080. A duplicate copy of this sheet is enclosed.
  ☒ Any filing fees under 37 CFR 1.16 for the presentation of extra claims.
  ☒ Any patent application processing fees under 37 CFR 1.17.
☒ Please charge any additional fees or credit any overpayments associated with this communication to our Deposit Account No. 12-0080. A duplicate copy of this sheet is enclosed. Applicants request any extensions of time necessary to respond.

I hereby certify that this transmittal letter and the papers referred to as being enclosed therein are being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231 on:

February 3, 2003
Date

DeAnn F. Smith, Esq., Reg. No. 36,683

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